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Benzene and Lymphohematopoietic Malignancies in Humans

Richard B. Hayes, DDS, PhD,[1]* Yin Songnian, MD,[2] Mustafa Dosemeci, PhD,[1] and Martha Linet, MD[1]

Background *Quantitative evaluations of benzene-associated risk for cancer have relied primarily on findings from a cohort study of highly exposed U.S. rubber workers. An epidemiologic investigation in China (NCI/CAPM study) extended quantitative evaluations of cancer risk to a broader range of benzene exposures, particularly at lower levels.*

Methods *We review the evidence implicating benzene in the etiology of hematopoietic disorders, clarify methodologic aspects of the NCI/CAPM study, and examine the study in the context of the broader literature on health effects associated with occupational benzene exposure.*

Results *Quantitative relationships for cancer risk from China and the U.S. show a relatively smooth increase in risk for acute myeloid leukemia and related conditions over a broad dose range of benzene exposure (below 200 ppm-years mostly from the China study and above 200 ppm-years mostly from the U.S. study).*

Conclusions *Risks of acute myeloid leukemia and other malignant and nonmalignant hematopoietic disorders associated with benzene exposure in China are consistent with other information about benzene exposure, hematotoxicity, and cancer risk, extending evidence for hematopoietic cancer risks to levels substantially lower than had previously been established.* Am. J. Ind. Med. 40:117–126, 2001. *Published 2001 Wiley-Liss, Inc.*†

KEY WORDS: benzene; leukemia; exposure assessment; lymphohematopoietic malignancies; epidemiology

INTRODUCTION

From the 1970s to the mid-1980s, scientists at the Chinese Academy of Preventive Medicine investigated health effects of benzene (CAPM Study). Since 1987, the U.S. National Cancer Institute (NCI) has collaborated with the Chinese Academy of Preventive Medicine in a large-scale epidemiologic study of cancer risk among workers exposed to benzene in China (NCI-CAPM Study). Recent commentaries [Wong, 1998, 1999; Budinsky et al., 1999] have raised questions about several aspects of the National Cancer Institute/Chinese Academy of Preventive Medicine (NCI/CAPM) cohort study, including methodologic aspects of exposure assessment, the wide range of hematopoietic disorders reported to be associated with benzene exposure, and the appropriate interpretation of the data in the light of the entirety of the scientific literature on health effects of benzene exposure. We review the evidence implicating benzene in the etiology of an array of hematopoietic disorders, clarify methodologic aspects of the approach used in the NCI/CAPM study, and examine the NCI/CAPM study in the context of the broader literature on health effects associated with occupational benzene exposure.

[1]Division of Cancer Epidemiology and Genetics, U.S. National Cancer Institute, Bethesda, Maryland 20892
[2]Chinese Academy of Preventive Medicine, Beijing, China
*Correspondence to: Richard B. Hayes, EPS 8114, National Cancer Institute, Bethesda, MD 20892. E-mail: hayesr@mail.nih.gov

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BENZENE AND HEMATOPOIETIC AND LYMPHOPROLIFERATIVE DISORDERS

Benzene Exposure Causes Acute Nonlymphocytic Leukemia

A scientific consensus concluded in 1982 that benzene was etiologically related to the development of acute nonlymphocytic leukemia based on epidemiologic studies [IARC, 1982]. Subsequent studies [Aksoy, 1985; McCraw et al, 1985; Bond et al, 1986; Wong et al, 1986; Rinsky et al, 1987; Wong, 1987a,b; Yin et al, 1996; Hayes et al, 1997; Rushton and Romaniuk, 1997] and meta-analyses [Austin et al, 1988; Swaen and Meijers, 1989] have confirmed that benzene causes leukemia, and may play a role in other lymphohematopoietic malignancies [Savitz and Andrews, 1997].

Two studies have shown that leukemia risk increases with increasing levels of benzene exposure [Rinsky et al., 1987; Hayes et al., 1997]. In the first of these studies, a cohort of 1,165 U.S. Caucasian males employed in the manufacture of a natural rubber film (rubber hydrochloride, which is also known as 'Pliofilm') during 1936–65 and followed up through 1981 experienced an increased mortality from leukemia (SMR = 3.37, based on 9 observed vs. 2.7 expected deaths). Risks also rose with increasing cumulative exposures in a dose-dependent manner [Rinsky et al., 1987). Wong [1995], using exposure estimates derived by NIOSH [Rinsky et al., 1987], showed highly significant 27-fold (95% confidence interval [CI]: 3–98) and 98-fold (95%CI: 20–288) increases in risk for AML among workers with, respectively, 200–400 and >400 ppm-years of cumulative benzene exposure (Fig. 1, Panel A).

Wong [1995] and Budinsky et al. [1999] suggest that the absence of demonstrated risk at lower levels of exposure is evidence for an exposure threshold below which benzene exposure is safe. In fact, the data from the Pliofilm cohort are essentially uninformative at doses below 200 ppm-years. As evidenced by 95% confidence intervals on the risk estimates, exposures below 200 ppm-years are consistent

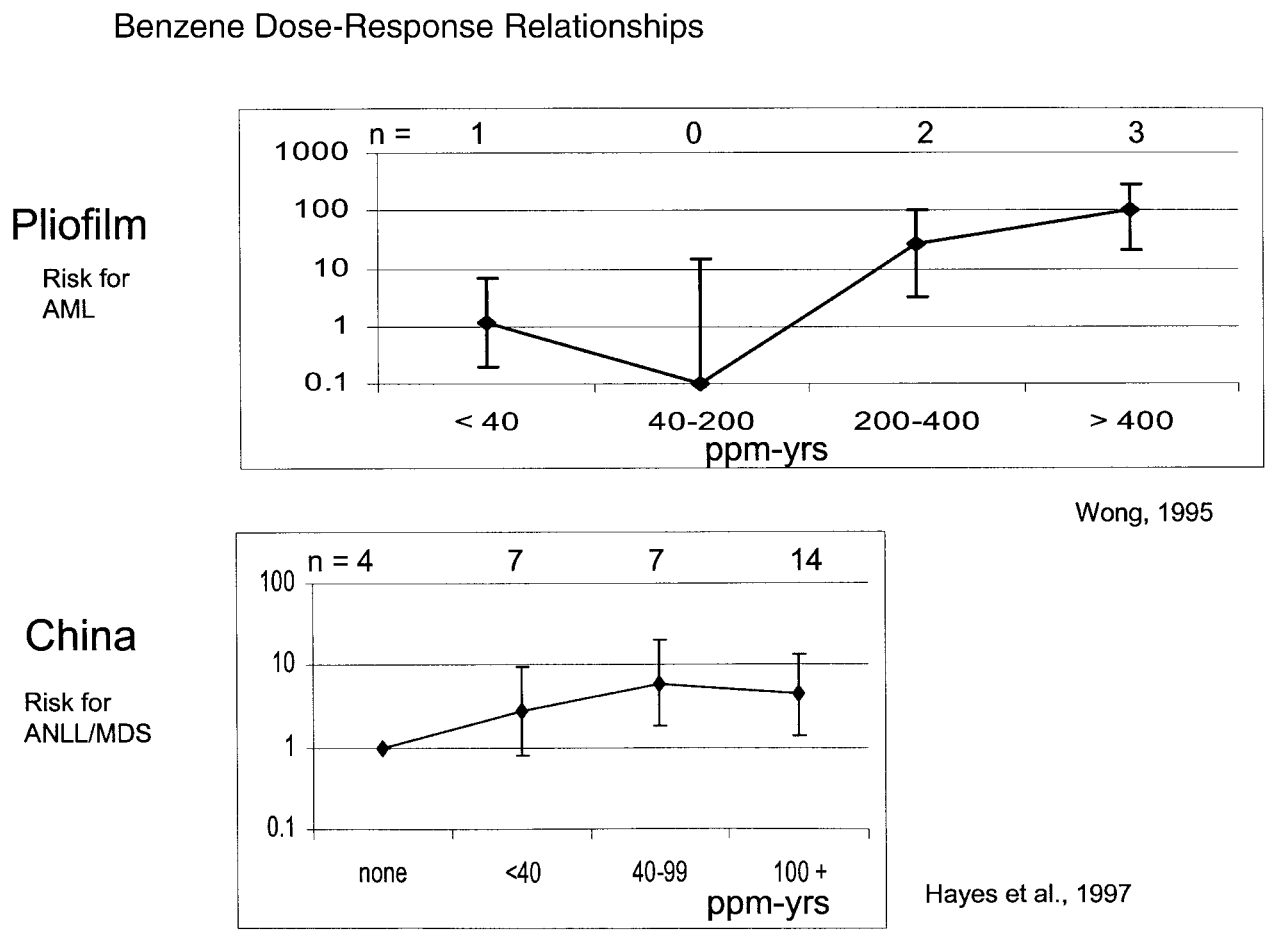

FIGURE 1. Benzene dose-response relationships.

with increases in risk for AML as great as 6–14-fold or, for that matter, with strongly protective effects (SMR $<<1.0$) (Fig. 1, Upper Panel).

In the second study, a cohort of 74,828 benzene-exposed workers employed from 1972 through 1987 in 12 cities in China showed incidence risks that were significantly increased for the combined grouping of all hematopoietic and lymphoproliferative malignancies (HLD) (RR = 2.6, based on 58 incident cases in the benzene-exposed group vs.13 in the unexposed group) and for total leukemia (RR = 2.5, based on 38 exposed cases), ANLL (R = 3.0, based on 21 exposed cases), and the combined category of acute myeloid leukemia plus the precursor myelodysplastic syndromes (ANLL/MDS) (RR = 4.1, based on 28 exposed cases) [Hayes et al., 1997].

The NCI–CAPM epidemiologic study in China [Hayes et al., 1997] was conducted to evaluate risks over a broader range of benzene exposures than was possible in the Pliofilm study. The NCI-CAPM study provides evidence that cumulative benzene exposure of less than 200 ppm-years is associated with increased risk for ANLL. Significant excesses of ANLL and ANLL/MDS were observed at average exposures of less than 25 ppm, with evidence of a doubled risk for ANLL/MDS at average exposure levels under 10 ppm benzene. Data from China (Fig. 1, Lower Panel) provide a quantitative assessment of benzene-associated cancer risks at levels of exposure above those now encountered in the U.S., but well below the high exposures which could be adequately assessed statistically in the Pliofilm facilities. Given the relatively small number of leukemia cases in either study and the differences in study methodology, a comparison of the two panels in Figure 1 shows a relatively smooth increase in risk over a broad dose range of exposures to benzene (below 200 ppm-years mostly from the China study and above 200 ppm-years mostly from the Pliofilm study).

Cytogenetic Effects of Benzene and its Metabolites

Observations on the cytogenetic effects of benzene support the findings on hematologic malignancy. Studies in benzene-exposed occupational groups [Yardley-Jones et al., 1990; Nise et al., 1991; Sasiadek, 1992; Tompa et al., 1994] have shown an elevated frequency of chromosomal aberrations in workers exposed to a range of benzene levels. Frequency of chromosomal aberrations in peripheral lymphocytes increases with increasing exposure to benzene [Zhang et al., 1998; Smith and Zhang 1998]. Some of the cytogenetic abnormalities observed (e.g., long arm deletions of chromosomes 5 and 7, aneuploidy in chromosomes 8 and 21) are similar to those observed in patients with secondary leukemias induced by alkylating agents and topoisomerase II inhibitor chemotherapy drugs [van Leeuwen, 1996; Felix, 1998], and by persons developing solvent-induced leukemias [Crane et al., 1996; Davico et al., 1998]. Several activated benzene metabolites (including phenol, 4,4′-biphenol, 2,2′-biphenol, hydroquinone, catechol, 1,2,4-benzenetriol, 1,4-benzenequinone, and *trans-trans*-muconaldehyde) have been shown to inhibit topoisomerase II, an enzyme critical in DNA replication and repair [Chen and Eastmond, 1995; Frantz et al., 1996; Eastmond et al., 2000]. Studies in animals and humans have shown that benzene induces deletions and other large-scale chromosomal alterations [Schiestl et al., 1997; Zhang et al., 1998; Eastmond et al., 2000], translocations [Aksoy, 1988; Chen et al., 1994; Smith et al., 1998; Eastmond et al., 2000], and aneuploidy [Chen et al., 1994; Zhang et al., 1996; Smith et al., 1998; Zhang et al., 1998]. Some evidence has demonstrated that benzene can induce point mutations or intragenic lesions [Rothman et al., 1995; Provost et al., 1996]. The relevance of these in vivo and in vitro observations to carcinogenesis has become apparent as cohorts with elevated frequencies of chromosomal aberrations in the Nordic countries, Italy, and Taiwan [Hagmar et al., 1994; Bonassi et al., 1995; Hagmar et al., 1998; Liou et al., 1999] have been observed to develop an increased occurrence of cancer, including hematopoietic and lymphoproliferative malignancies [Bonassi et al., 1995]. These various lines of evidence suggest that induction of chromosomal alterations by benzene is likely to play an important role in leukemogenesis and other genotoxic effects.

Hematotoxic Effects of Benzene

Chinese workers have been found to exhibit signs of hematotoxicity at average benzene exposure levels below 31 ppm [Rothman et al., 1996]. Differential sensitivity of CD4 vs. CD8 lymphocytes was observed [Lan et al., 2001]. Hematotoxicity was documented at levels as low as 10 ppm among the U.S. pliofilm workers [Ward et al., 1996]. Some animal studies [Baarson et al., 1984], but not all [Cronkite et al., 1985, 1986], have shown significantly reduced lymphocyte counts at benzene exposure levels of 10 ppm. In China, confirmed benzene-induced chronic hematotoxicity (a total white blood less than 4,500/cu mm for at least 6 months) [Chinese Ministry of Public Health, 1994] was associated with a 42-fold increased risk of developing MDS or other HLD [Rothman et al., 1997]. The epidemiologic studies of benzene toxicity, supported by extensive toxicologic data [Chen and Eastmond, 1995; Smith and Zhang, 1998; Golding and Watson, 1999; Smith and Rothman, 2000], strongly suggest that cytogenetic and other genotoxic damage in circulating lymphocytes and hematotoxicity represent important early biologic effects of benzene exposure.

When concluding that a threshold benzene concentration exceeding 50–75 ppm is necessary to induce mild

to modest declines in total white blood cell counts, Budinsky et al. [1999] misinterpret earlier reports [Kippen et al., 1989; Cody et al., 1993] and fail to consider more recent evidence [Rothman et al., 1996; Ward et al., 1996]. As with benzene-associated risk for leukemia, there is no clear evidence of a threshold below which benzene does not cause hematotoxicity in humans [Rothman et al., 1996; Ward et al., 1996].

Benzene and Hematopoietic and Lymphoproliferative Disorders Other Than ANLL

Aplastic anemia

Aplastic anemia is a disorder characterized by peripheral pancytopenia and marrow hypoplasia. The pathogenesis is poorly understood, but immunologic destruction or suppression of hematopoietic cells seem to characterize the majority of patients with severe aplastic anemia [Guinan, 1997]. Numerous clinical reports [IARC, 1982; Aksoy, 1988, 1989; Young and Alter, 1994], as well as survey data from studies of Turkish and Chinese workers [Aksoy et al, 1971; Yin et al, 1987], and cohort follow-up studies [Aksoy and Erdem, 1978; Paci et al, 1989; Yin et al, 1996] have linked aplastic anemia with benzene exposure. The association is well-established, with the incidence as high as 100 per 100,000 person-years at benzene exposure levels above 100 ppm [Smith, 1996].

Myelodysplastic syndromes [MDS]

Recognized as a clinical entity only in recent decades, myelodysplastic syndromes are clonal disorders of the marrow with impaired differentiation and increased risk of transformation to acute leukemia [Bennett et al., 1982; Kouides and Bennett, 1997]. Although morphologic criteria for MDS were published by the French-American-British expert hematologists group in 1982, population-based data are generally lacking except for regions covered by specialist hematology registries [Cartwright et al., 1997]. Significantly elevated risks of MDS were found in the China benzene cohort [Yin et al., 1996]. It is noteworthy that each Chinese worker ultimately determined to have MDS was initially diagnosed as having ANLL; only upon review by NCI/CAPM expert hematologists was it recognized that the correct diagnosis was MDS [Travis et al., 1994]. Early clinical reports described benzene-exposed workers who developed ANLL that was preceded by pancytopenia, and characterized by abnormalities of bone marrow and peripheral blood [Goguel et al., 1967; Aksoy and Erdem, 1978; Van den Berghe et al., 1979]. Some cases of MDS have been reported among persons exposed to solvents [Vineis et al., 1990] and benzene [Ciccone et al., 1993]. A case-control study in Britain reported an association of MDS with exposure to gasoline, diesel fumes, or liquids [Farrow et al., 1989]. Excess occurrence of MDS was observed during 1985–89 among workers at a petroleum manufacturing and refining plant in conjunction with a deficit in leukemia among the same occupational group [Cowles et al., 1991; Honda et al., 1995]; during 1940–84, however, excesses of leukemia were found in workers from this plant [McCraw et al., 1985; Austin et al., 1986; Wongsrichanalai et al., 1989]. The investigators postulated that changes in diagnostic or reporting practices might explain the shift from leukemia to MDS. MDS precedes AML in a majority of patients developing secondary treatment-related leukemias [van Leeuwen, 1996].

The cytogenetic abnormalities seen in benzene-exposed workers [Smith et al., 1998; Zhang et al., 1998] have also been identified among persons with treatment-related MDS [van Leeuwen, 1996; Felix, 1998], thus suggesting a similar mechanism of pathogenesis as that occurring in treatment-related AML/MDS.

Leukemias other than ANLL

Chronic myeloid leukemia [CML] has been linked with benzene exposure in clinical reports [Tareef et al., 1963; Browning, 1965; Dean, 1996; Siena et al., 1999], a small case-control study [Goguel et al., 1967], the cohort of Chinese workers followed up through 1981 by the Chinese Academy of Preventive Medicine [Yin et al., 1987, 1989], and the expanded cohort of Chinese workers follow-up through 1987 by the NCI-CAPM collaborators [Yin et al., 1996]. Expert hematopathology review of CML cases among the Chinese benzene-exposed workers revealed dysplasia in peripheral blood and bone marrow, with undifferentiated blasts comprising approximately 30–35% of bone marrow cells, bone marrow basophilia, and low serum leukocyte alkaline phosphatase [Travis et al., 1994]. Excesses of acute lymphoid leukemias have been described in some populations of benzene-exposed workers in the United Kingdom [Rushton and Rominiuk, 1997] and China [Yin et al., 1996]. Increased risks of lymphocytic leukemia were reported among rubber workers [McMichael et al., 1976; Wolf et al., 1981; Arp et al., 1983; Checkoway et al., 1984], and chronic lymphocytic leukemia in long-term petroleum industry workers [Bertazzi et al., 1989; Wong and Raabe, 1989; Wongsrichanalai et al., 1989]; both occupational groups are believed to be exposed to benzene.

Lymphomas

Limited data suggest that lymphomas might be associated with benzene exposure. Elevated risk of Hodgkin's disease has been reported in a few cohorts of rubber industry

workers [McMichael et al., 1976; Andjelkovich et al., 1977; Bernardinelli et al., 1987], although misclassification of non-Hodgkin's lymphoma incorrectly diagnosed as Hodgkin's disease was not uncommon prior to improvements in histological diagnosis in the 1970s [Banks, 1992]. Case-control studies [La Vecchia et al., 1989; Blair et al., 1993] have suggested a relationship between benzene and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma was increased 3-fold among the Chinese benzene-exposed workers, with risks rising to 4-fold for workers with 10 or more years of benzene exposure [Hayes et al., 1997]. It may be noteworthy that lymphocytes in peripheral blood have been found to be the most sensitive hematological cell type to benzene exposure [Rothman et al., 1996], showing declines at exposure levels as low as 10 ppm among the U.S. Pliofilm workers [Ward et al., 1996].

Multiple myeloma

Few analytic investigations have linked multiple myeloma with benzene exposure [Decoufle et al., 1983; Rinsky et al., 1987]. The significant excess observed in the initial follow-up of Pliofilm workers was not found by Paxton et al. [1994a,b], however, a biased study group may have been included for the earliest years of their data analysis. The relationship of benzene with risk of multiple myeloma has been the subject of recent commentaries [Bergsagel et al., 1999, 2000; Goldstein and Shalat, 2000]. Multiple myeloma is rare, making it difficult to assess risk in epidemiologic studies.

METHODS IN THE NCI/CAPM STUDY

The NCI–CAPM study extends epidemiologic data to exposure levels not adequately investigated in the past. In the commentaries of Budinsky et al. [1999] and Wong [1999] several issues were raised about methods used in the NCI–CAPM study.

Exposure Assessment in the NCI–CAPM Study

It was argued that the exposure assessment procedure used in the NCI–CAPM study misclassified large numbers of highly exposed workers as having low levels of exposure and, specifically, that the exposure assessment approach did not adequately consider workers with high-dose exposures [Budinsky et al., 1999; Wong, 1999].

The procedures for benzene exposure estimation have been described in detail [Dosemeci et al., 1994; Yin et al., 1994]. Briefly, factory exposure assessment teams consisting of industrial hygienists, safety officers, and other employees used a standardized methodology to assign a factory- and work unit-specific exposure for each specific job title for each of seven calendar periods (1949–59, 1960–64, 1965–69, 1970–74, 1975–79, 1980–84, 1985+). One of six benzene exposure level categories (<1 ppm; 1–5 ppm; 6–10 ppm; 11–25 ppm; 26–50 ppm; and >50 ppm) was assigned, using abstracted factory record information on benzene use and working conditions in conjunction with available air measurements of benzene (n = 8,477). The historical benzene exposure measurements were short-term ''grab'' samples, and served only as one component of the data used for exposure assessment, with consideration that these sample measurements were not collected for epidemiologic purposes and often do not represent usual exposure conditions. Other data abstracted for exposure assessment included amount of benzene-containing materials used, percent of benzene in the materials used, the average daily frequencies of benzene exposure, historical changes in engineering controls, use of personal protective equipment, and occurrence of changes in other control measures.

For illustrative purposes in one of our publications [Dosemeci et al., 1994], the results of this detailed effort were summarized across all study factories and presented as average estimated levels for each major industry [Table III in Dosemeci et al., 1994] and occupation group [Table IV in Dosemeci et al., 1994]. Wong's [1999] conclusion that this summary data was used to estimate factory work-unit, calendar-specific exposures is incorrect. Consequently his conclusion that this use led to a systematically underestimated historical exposures in the NCI/CAPM study is also incorrect. By our estimates, 27% of the person years in the NCI/CAPM study were contributed by workers with average exposures of 25 ppm or greater, and about 40% of person-years were accumulated among subjects with cumulative exposures of 100 ppm-years or greater [see Table II in Hayes et al., 1997].

Budinsky et al. [1999] and Wong [1999] have argued that the exposure estimates assigned to the Chinese benzene workers in the NCI/CAPM study [Dosemeci et al., 1994] are in substantial disagreement with the true values based on other published data from studies carried out in China [Inoue et al., 1989; Rothman, et al., 1996]. The specific workplaces chosen for these two cross-sectional investigations of toxic effects of benzene were selected to provide data for workers with a range of exposures in order to assess toxic effects. It is completely without basis to conclude that the exposures in these specially chosen small number of workplaces would be in any sense reflective of those found in the 672 factories in our study. This argument is analogous to the concluding that the exposures in the factories included in the Pliofilm study [Rinsky et al., 1987] were reflective of the general historical occupational exposures to benzene in the United States.

Budinsky et al. [1999] and Wong [1999] have also compared exposure data reported for the NCI–CAPM study

[Dosemeci et al., 1994] with benzene exposure measurements reported for workplaces in which leukemia occurred in the earlier CAPM study [Yin et al., 1987, 1989]. As clearly documented in the description of the exposure assessment approach employed in the NCI–CAPM study, the calendar time-specific exposure assessment utilized all available exposure information abstracted as listed above. In comparing the air monitoring data reported for the cases of leukemia identified in the CAPM study [Yin et al., 1987, 1989] to the more comprehensively derived exposure estimates developed for the NCI–CAPM study [Hayes et al., 1997], several caveats should be considered. First, the NCI–CAPM study followed a specific exposure assessment protocol, whereas the rules for inclusion of historical benzene results in the earlier CAPM studies were not systematized. Second, the historical air monitoring results reported in the earlier CAPM studies represent the estimated work area exposure at a single point in time, and may have been collected for any of a number of reasons not related to individual average exposure assessment. Third, the NCI–CAPM study included an expanded number of factories employing 74,828 benzene-exposed workers, who were followed up into more recent years [1972–87] when average benzene levels had declined [Yin et al., 1994], compared to the smaller number of factories employing 28,460 benzene-exposed workers followed up for 6 fewer years (1972–81) in the earlier study carried out by the CAPM [Yin et al., 1987, 1989]. Budinsky et al. also point out what these authors believe to be discrepancies in average estimated benzene exposures for workers with leukemia in a first report of findings from the CAPM study [Table IV in Yin et al., 1987] and a subsequent report of the CAPM cohort [Table V in Yin et al., 1989]. These discrepancies are cited as demonstrating a lack of rigor in data collection, which is implied as extending to the NCI–CAPM exposure evaluation. The discrepancy is due, however, simply to reporting exposure in the first CAPM paper based on exposure measures in the respective workplaces taken before, during and after employment of the leukemia case [Yin et al., 1987] and reporting exposures in the second paper solely for time-periods during the patient's employment in the study factory [Yin et al., 1989]. Regardless, the exposure estimates and other exposure-related information ascertained in the CAPM study per se were not used for the exposure assessment carried out in the NCI–CAPM study.

Although there are substantial differences between the CAPM and the NCI–CAPM studies, there is overlap in study populations. Thus, within broad limits, one would expect some concordance in the distribution of exposures in the two investigations. In Table I are shown benzene exposure data [average exposure and cumulative exposure] for the workers in the CAPM study and in the NCI–CAPM study who developed leukemia and MDS. [For the NCI–CAPM study, MDS is included with leukemia since each of the workers developing MDS was originally classified in China as having ANLL. There were no workers reported as developing MDS in the CAPM study. We also show results for total leukemia, following Budinsky et al. [1999, Table VI].

A greater proportion of cases in the CAPM study [Yin et al., 1989] were highly exposed than in the NCI–CAPM study [Hayes et al., 1997]. This is not entirely surprising as the CAPM investigation was carried out in an earlier time period characterized by higher exposures among workers and proportionally more factories with high exposure. Budinsky et al.[1999] and Wong [1999] are concerned about a substantial shift of highly exposed workers in the CAPM study to assignment at lower exposure categories in the NCI–CAPM study. As shown in Table I, there are two more cases at the highest level of average exposure in the CAPM study than in the NCI–CAPM study and no greater number of subjects in the highest category of cumulative exposure. These differences demonstrate no evidence of a systematic bias toward lower exposure classification in the NCI–CAPM study.

TABLE 1. Comparison of Exposure Estimates for Leukemia Cases in the CAPM [Yin et al., 1989] and NCI–CAPM Studies [Hayes et al., 1997]

	Leukemia/MDS			
	CAPM		NCI–CAPM	
Exposure-dose parameter	N	%	N	%
Average ppm				
<10	7	25	19	42
10–24	6	21	13	29
>=25	15	54	13	29
ppm-Year				
<40	8	29	13	29
40–99	2	7	10	22
>=100	18	64	22	49
Total	28		45	
	ANLL/MDS			
Average ppm				
<10	6	30	11	39
10–24	4	20	9	32
>=25	10	50	8	29
ppm-Year				
<40	6	30	7	25
40–99	2	10	7	25
>=100	12	60	14	50
Total	20		28	

Potential Confounding in the NCI–CAPM Study

In the NCI–CAPM study, elevated risks were observed for ANLL/MDS and other malignant and benign hematopoietic conditions among workers exposed to benzene. Lifestyle factors could confound an occupational association with disease if the confounding factor were causally associated with the disease and correlated with the study exposure. For ANLL there are no obvious lifestyle confounding factor candidates, except possibly cigarette smoking, which has been associated in some studies with an approximately 50% increase in leukemia risk [Linet and Cartwright, 1996]. As demonstrated in other settings [Axelson and Steenland, 1988; Siemiatycki et al., 1988], it is improbable that tobacco use correlates sufficiently strongly with benzene exposure in our study population to account for the dose-related effects attributed to benzene. The exposed and unexposed groups in our study derived from similar occupational backgrounds; there is no evidence that differential lifestyle factors, such as tobacco use, could account for benzene-associated risk differences.

The workers in this investigation may have been exposed to chemicals other than benzene; in principle, the observed excesses for ANLL could be due to these alternative chemical exposures. However, risks for ANLL/MDS were systematically increased across the spectrum of industries studied [Hayes et al., 1997], arguing that these associations were due to the common exposure to benzene and not to other industry-specific exposures. Other exposures that could account for this pattern are not evident. The only other industrial exposure that has consistently been linked to ANLL/MDS or other hematopoietic disorders is ionizing radiation, and ionizing radiation was not an occupational exposure in the NCI-CAPM study factories. Based on industry and occupation data collected during the cohort follow-up investigation, other suspect leukemogens, such as butadiene and ethylene oxide [Linet and Cartwright, 1996], are unlikely to contribute significantly to our overall study results. Most of the Chinese benzene-exposed workers were painters who used benzene-containing paints. Elevated risks for ANLL were found in this group, however, painters not exposed to benzene do not typically show increased risks for leukemia [IARC, 1989].

A Dose-Response for Benzene Poisoning Indirectly Validates the Exposure Assessment in the NCI–CAPM Study

While lympho-hematopoietic malignancies were relatively rare in the Chinese cohort, we identified 412 workers with chronic benzene poisoning in 11 of the 12 study cities. We reasoned that this large number of subjects with a disease known to be due to benzene would provide an opportunity to indirectly validate our benzene exposure assessment procedure [Dosemeci et al., 1996]. Our finding of a clear dose-response for benzene poisoning [RR = 1 (referent), 2.2, 4.7, and 7.2 for recent benzene exposures of <5 ppm, 5–19 ppm, 20–39 ppm, and 40+ ppm, respectively] suggested the predictive capacity of the exposure assessment approach. This result also suggests a degree of accuracy in quantitative estimation of benzene exposure, as successful ranking was only possible if quantitative estimates were concordant. The alternative and, in our view, the substantially weaker explanation for the observed dose-response relationship is that exposure estimates for benzene were incorrectly assigned; however, these assignments of incorrect levels would have had to have been carried out with a similar degree and direction of error in each of the 12 cities.

SUMMARY AND CONCLUSIONS

Benzene is an established cause of acute nonlymphocytic leukemia, aplastic anemia, and benzene poisoning [hematotoxicity] and may cause other lymphohematopoietic malignancies and related conditions. The Pliofilm study [Rinsky et al., 1987] provided quantitative estimates of leukemia risk at high levels of benzene exposure. The NCI/CAPM study extended quantitative estimates of risk to lower levels of exposure below 10 ppm. Although the NCI–CAPM study and all other retrospective investigations have limitations, the criticisms raised by Budinsky et al. and Wong do not negate the findings that significantly elevated risks for lymphohematopoietic disorders occurred at average levels of benzene exposure substantially below those identified in the Pliofilm cohort. Internationally, many thousands of men and women, particularly in developing economies, are exposed to benzene at levels associated in the NCI–CAPM study with leukemogenesis and other types of HLD.

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